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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/756,978	01/09/2001	Eugene Roussel	210582.0001/1US	6809

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EXAMINER

YU, MISOOK

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 11/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application N .

09/756,978

Applicant(s)

ROUSSEL, EUGENE

Examiner

MISOOK YU, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 August 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-66 and 81-83 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-66, 81-83 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other:

DETAILED ACTION

The amendment filed on 08-13-2003 is acknowledged. Claims 11, and 12 are amended, and claims 81-83 are new. Claims 1-66, and 81-83 are pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claim Rejections - 35 USC § 112

Claims 2, and 4-6 **remain rejected** for reason of record under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to method of inducing cancer cell death in a human patient using proteases plus three other agents. This rejection is based on use of protease in inducing cancer cell death.

Applicant argues that it is immaterial whether a protease will induce tumor cell death as long as the other portions of the claimed method are performed. This and other arguments have been fully considered but found unpersuasive because the art (note previously provided Dabrowska et al, Kondoh et al, or Yamamoto et al) indicates that protease helps cancer to be metastasized. The specification does not teach what dose(s) of a protease will contribute leukocyte recruitment and activation and enhancing the type 1 inflammatory response instead of helping tumor to be metastasize into another location. The Office does not understand why applicant dismisses the critical element of invention as "immaterial". Applicant's attention is directed to the dependent

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claims 4-6, which indicate how to use protease is critical part of the invention. The specification fails to provide a sufficient guidance what is the effective dose for accomplishing the purpose stated in the preamble of the claims. Considering the state of art, no guidance in terms of effective dose, no working example, it is maintained that one skilled in the art would have reasons to question the efficacy of the claimed treatment method. In the absense of a working example or other evidence of using protease's effectiveness in cancer treatment, it is maintained that undue experimentation would be required to practice the invention as claimed.

Claim Rejections - 35 USC § 103

Claims 1, 3, 13-17, 19, 20, 25-29, and 31-39 remain rejected for reason of record and the new claims 81-83 are also rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (J Immunol. 2000 Jan 1: 164: 231-9) in view of Tannenbaum et al (J Immunol. 1998: 161: 927-932) or Lanni et al (Proc Natl Acad Sci USA vol. 94, pages 9679-83).

The claims are drawn to method of human cancer treatment by local administration of four active ingredients i.e., 1) antigen-releasing agent 2) leukocyte attractant 3) interferon gamma 4) a second type 1 inflammatory response promoting agent.

Applicant argues every element of claims is not taught in the art of record because the art does not teach local administration of IFN-g or leukocyte attractant to a tumor in any animal but this argument is not persuasive because Lee reference teaches local administration of anti-cancer agent as "peritumorally" at page 232, right column,

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lines 5. Since the preferred embodiment specified at page 25, line 4 of the instant application says the agent(s) is also injected at “the tumor periphery”, “peritumorally” of Lee reference is same as the limitation “locally administering” in the instant claims. Lee reference teaches that “locally administering to a tumor” is a well known technique in the art before the effective filing date of the instant application. Since injection of one anti-tumor agent peritumorally is taught by the art well before the effective filing date of the instant application, injecting other anti-tumor agents peritumorally is an obvious variation and well within reach of one in ordinary skill in the art and can be accomplished with a reasonable expectation of success. Applicant does not argue that other agents could not have been administered locally to a tumor due to an art-known technical difficulty before the effective filing date of the instant application, and applicant does not appear to overcome such difficulty faced in the art in the instant application.

Applicant argues that there is no motivation to combine references and no reasonable expectation of success to achieve the synergy. This argument has also been fully considered but found not persuasive, either because the instant specification does not disclose any synergy ($1+1>2$). The specification does not disclose any comparison data to show synergy. However, Lee et al at Fig. 1C at page 233 teach synergy that combinational effect is greater than addition of individual component in that the anti-Fas antibody alone does not kill any cancer cells but the anti-Fas antibody (one of “antigen-releasing agent”) in combination with IFN-gamma, and TNF (“a second type 1 inflammatory response promoting agent”) has the highest anti-tumor effect. This teaching suggests combination of the three is desirable for cancer treatment. All of the

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products in the instant claims are known in the art, and how to make and use said products as well as combinational cancer therapy are all known in the art. All the active steps performed by hand of man are also known in the art. As the prosecution history indicates, all of the products in the instant claims have been shown to have good effects in cancer treatment and/or for cancer patients. The Office maintains that one of ordinary skill would have been able to practice the instant invention with reasonable expectation of success before the effective filing date of the instant application.

Claims 7-9 remain rejected for reason of record under 35 U.S.C. **103(a)** as being unpatentable over Lee et al (J Immunol. 2000 Jan 1: 164: 231-9) in view of Tannenbaum et al (J Immunol. 1998: 161: 927-932) or Lanni et al (Proc Natl Acad Sci USA vol. 94, pages 9679-83) as applied to claim 3 above, and further in view of Zeisig et al (provided with Dr. Roussel's Declaration filed on 1-14-2003, Paper No. 19; Anticancer Research, 1994, vol. 14, page 1785-1790).

The claims are drawn to the method of the base claim using the specific products in the instant claim. Applicant does not argue.

Claim 10 remain rejected under 35 U.S.C. **103(a)** as being unpatentable over Lee et al (J Immunol. 2000 Jan 1: 164: 231-9) in view of Tannenbaum et al (J Immunol. 1998: 161: 927-932) or Lanni et al (Proc Natl Acad Sci USA vol. 94, pages 9679-83) as applied to claim 3 above, and further in view of Chou et al (1997, Bioelectromagnetics, vol. 18, page 14-24, abstract only) or Habal (1980, J Biomer Mater Res, vol. 14, pages

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789-801, abstract only), Jaroszeski et al (1997, Biochim Biophys Acta, vol. 1334, pages 15-18), or Wemyss-Holden et al (2000, J Surg Res, vol. 93, pages 55-62).

The claims are drawn to the method of the base claim (see above) using electric current as antigen releasing agent. Applicant does not argue that the electric current has been used cancer treatment.

Claim 11 and 12 are rejected under 35 U.S.C. **103(a)** as being unpatentable over Lee et al (J Immunol. 2000 Jan 1; 164: 231-9) in view of Tannenbaum et al (J Immunol. 1998; 161: 927-932) or Lanni et al (Proc Natl Acad Sci USA vol. 94, pages 9679-83) as applied to claim 3 above, and further in view of Tamai et al (2000, Oncol Rep, vol. 719, pages 719-23).

The claims are drawn to the method of the base claim (see above) using either acid or base as antigen releasing agent. Applicant does not argue that Tamai et al teach either use of strong base or acid in cancer treatment method. The reference also gives guidance about what concentration of acid is appropriate and therefore the acid in instant claim 11 is obvious variation of the acid in the prior art since the instant specification does not teach any unexpected result with the recited specific acids. Combining known anti-tumor therapy for inducing tumor cell death is obvious.

Claims 17 and 18 are rejected under 35 U.S.C. **103(a)** as being unpatentable over Lee et al (J Immunol. 2000 Jan 1; 164: 231-9) in view of Tannenbaum et al (J Immunol. 1998; 161: 927-932) or Lanni et al (Proc Natl Acad Sci USA vol. 94, pages

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9679-83) as applied to claim 1 above, and further in view of Wuyts et al (provided with Dr. Roussel's Declaration filed on 1-14-2003, Paper No. 19, 1994, Journal of Immunological Methods, vol. 174, pages 237-247).

The claims further specify leukocyte attractant of the base claim. Applicant does not argue that Wuyts et al teach various proteins specified in the instant claims as leukocyte attractant.

Claims 30, and 40-66 are rejected under 35 U.S.C. **103(a)** as being unpatentable over Lee et al (J Immunol. 2000 Jan 1; 164: 231-9) in view of Tannenbaum et al (J Immunol. 1998; 161: 927-932) or Lanni et al (Proc Natl Acad Sci USA vol. 94, pages 9679-83) as applied to claims 1, 3, 13-17, 19, 20, 25-29, and 31-39 above, and further in view of Greenberg (1997, provided with Dr. Roussel's Declaration filed on 1-14-2003, Paper No. 19), Parslow (1997, provided with Dr. Roussel's Declaration filed on 1-14-2003, Paper No. 19), Akatov et al (2000, provided with Dr. Roussel's Declaration filed on 1-14-2003, Paper No. 19), and Oppenheim et al (1997, provided with Dr. Roussel's Declaration filed on 1-14-2003, Paper No. 19).

Applicant does not argue that art teaches all of the products in the instant claims have either anti-tumor effects or good in patients going through anti-tumor therapy. Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use products good for anti-tumor therapy to induce cancer cell death. The specification does not teach any unexpected results, combining known compounds good for anti-tumor effects for inducing cancer cell death is obvious.

Double Patenting

Claim 82 is newly objected to under 37 CFR 1.75 as being a substantial duplicate of claim 1. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Only difference in claims 82 and 1 is the limitation "effective" in claim 82 in the second last line. However, claim 1 also require "effective" amount in order to induce the intended response.

Conclusion

No claim is allowed.

All other rejection(s) set forth in the Office action mailed 04-11-2003 is withdrawn.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

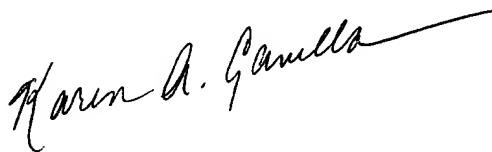
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the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 703-308-2454. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

A handwritten signature in black ink, appearing to read "Misook Yu", with a long, sweeping horizontal line extending to the right.

Misook Yu
November 21, 2003